77. *Preliminary Synthetic Experiments in the Morphine Group. Part V. Completion of the Synthesis of a Laudanosoline Dimethyl Ether related to Sinomenine.*

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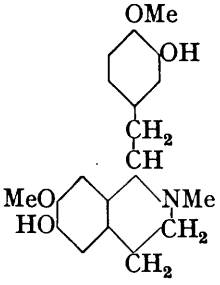
THE object of this investigation is sufficiently explained in Part I (J., 1931, 3164). The base (I), which is possibly *protosinomenine*, has now been characterised and analysed in the form of a *picrolonate*. Experiments on the possible transformation of the base into *dl*-sinomenine are in progress.



(I.)

We are gratified that Prof. C. Schöpf has indicated (*Annalen*, 1932, **497**, 22, 47, 59) his intention to work along the lines laid down in Part I of this series. It is highly probable that only a fortunate and partly fortuitous discovery will reveal the appropriate conditions for the transformation of laudanosine-types into bases containing a morphine-like nucleus; therefore we welcome efforts by other workers to realise our biogenetic schemes in practical synthesis.

ω-Nitro-3-benzyloxy-4'-methoxystyrene.—The prepn. (*loc. cit.*) has been improved. NH_2Me,HCl (0·2 g.) and dry Na_2CO_3 (0·2 g.) were added to a cold solution of *O*-benzyl*iso*vanillin (10 g.) and $MeNO_2$ (3 g.) in EtOH (100 c.c.), and the mixture kept for 3 days with occasional shaking. The yellow cryst. product, collected and washed with H_2O (10 g., m. p. 124—125°), was sufficiently pure for the next stage effected as described in Part I.

*6-Benzyloxy-7-methoxy-1-(3'-benzyloxy-4'-methoxybenzyl)-3 : 4-dihydro*isoquinoline.—The cyclisation of *O*-benzylhomo*iso*vanillo-β-(3-benzyloxy-4-methoxyphenyl)ethylamide, previously attempted unsuccessfully, has now been effected by the method of Gulland and Haworth and their collaborators (J., 1928, 581, 1132, 1834, 2083; 1929, 658; 1931, 2872, 2881, 2885, 2893; cf. Kondo and Ishiwata for a case in which $Ph{\cdot}CH_2{\cdot}O$ was present in the molecule, *Ber.*, 1931, **64**, 1533) depending on the use of PCl_5 in $CHCl_3$. When a mixture of dibenzylated amide (4 g.), $CHCl_3$ (40 c.c.), and PCl_5 (8 g.) was kept for 4 days, yellow clustered needles of the condensation product separated. The $POCl_3$ and PCl_5 were decomposed by addition of ice, and the $CHCl_3$ evaporated in vac. below 40°. The aq. layer was decanted from a dirty yellow solid, which was dissolved in hot EtOH (20 c.c.) and 2*N*-HCl (10 c.c.) added to the solution. On cooling, two layers separated : crystn. could be induced with difficulty in the upper layer, which was cooled in a freezing mixture; inoculation then facilitated slow crystn. from the lower layer also. The *hydrochloride* (3·5 g.), after being washed with HCl–EtOH aq., crystallised from the same solvent in slender clustered needles, m. p. 148—150° (Found in material dried in vac. over H_2SO_4 : C, 72·3; H, 6·2; N, 3·0; Cl, 6·9. $C_{32}H_{31}O_4N$,HCl requires C, 72·5; H, 6·0; N, 2·6; Cl, 7·0%), readily sol. in EtOH but sparingly sol. in H_2O.

The free base crystallised from EtOH–light petroleum in colourless needles, m. p. 105—110°; it was readily oxidisable and difficult to keep (Found in material dried at 50° : C, 75·2; H, 7·0; in material dried at 60° : C, 76·8; H, 6·8; N, 3·1; in material dried at 110° : C, 77·8; H, 6·7; N, 2·2. $C_{33}H_{35}O_4N,H_2O$ requires C, 75·2; H, 7·0; N, 2·7. $C_{33}H_{35}O_4N,0{\cdot}5H_2O$ requires C, 76·4; H, 7·0; N, 2·7. $C_{33}H_{35}O_4N$ requires C, 77·8; H, 6·9; N, 2·8%).

The *methiodide* was prepared from crude base which was isolated by means of Et_2O from a mixture of the hydrochloride in EtOH and 10% KOH aq., MeOH was used as diluent, and the formation of the methiodide was complete after 6 hrs.' refluxing. The salt crystallised from MeOH in yellow prisms, m. p. 198—200° after sintering at 163—164° (Found : C, 61·0; H, 5·4; N, 2·2; I, 20·2. $C_{33}H_{34}O_4NI,0{\cdot}5H_2O$ requires C, 61·5; H, 5·4; N, 2·2; I, 19·7%).

6-*Benzyloxy*-7-*methoxy*-1-(3′-*benzyloxy*-4′-*methoxybenzyl*)-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline.—The last-described methiodide (1·5 g.) was converted into the methochloride, a yellow gum, by means of AgCl. This was dissolved in EtOH (20 c.c.) and reduced by shaking with H after addition of a PtO_2–Pt catalyst (60 c.c. H absorbed in 30 min.; theory for 2H, 53 c.c.). The filtered liquid was concentrated in vac. and the amorphous residue was dissolved in the minimum of EtOH and added to 10% KOH aq. and much Et_2O. The Et_2O solution after evaporation afforded a pale yellow syrup (1·5 g.), which was dissolved in a little warm 60% MeOH and kept in the ice-chest. Pale yellow crystals (1·0 g., m. p. 85—87°) separated: the *base*, recryst. from EtOH aq., formed aggregates of colourless needles, m. p. 96—97° (Found: C, 76·8; H, 6·8; N, 3·1. $C_{33}H_{35}O_4N$ requires C, 77·8; H, 6·9; N, 2·8%). The low value for C is attributed to some loss of benzyl from the benzyloxy-groups; this has a very large effect.

6-*Hydroxy*-7-*methoxy*-1-(4′-*methoxy*-3′-*hydroxybenzyl*)-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (I).—Conc. HCl (5 c.c. sat. at 0°) was slowly added to a solution of the *O*-dibenzyl-*O*-dimethyl-laudanosoline (1·0 g.) in AcOH (50 c.c.) heated on the steam-bath. After 30 min. the liquid was boiled over a gauze for a few min., the AcOH then evaporated in vac., and the residue several times taken up in EtOH and evaporated in vac. In this way the hydrochloride was obtained as a yellow solid readily sol. in H_2O and EtOH but not crystallisable. The *picrolonate* was prepared in EtOH, separating slowly from a hot solution; it was recryst. from EtOH–AcOH (3 : 1) in yellow spindle-shaped crystals, m. p. 177—178° after sintering at 170—171° (Found: C, 58·5; H, 5·4; N, 11·9. $C_{19}H_{23}O_4N,C_{10}H_8O_5N_4$ requires C, 58·7; H, 5·2; N, 11·8%). This characteristic derivative is sparingly sol. in EtOH and readily sol. in hot AcOH.

The perchlorate crystallised from H_2O, containing a little EtOH, in colourless prisms, m. p. 107—108° with vigorous decomp., after sintering at 97—98°.

6-*Hydroxy*-7-*methoxy*-1-(3′-*benzyloxy*-4′-*methoxybenzyl*)-2-*methyl*isoquinolinium *Chloride*.—The related phenol-betaine, already described (Part I, *loc. cit.*), was obtained as before by the action of $Ba(OH)_2$ aq. on 6 : 7-dimethoxy-1-(3′-benzyloxy-4′-methoxybenzyl)-2-methyl*iso*quinolinium methosulphate, but it was found advantageous to treble the volume of H_2O prescribed. The phenol-betaine (1 g.), suspended in EtOH (10 c.c.), was mixed with conc. HCl (*ca.* 1 c.c.) and H_2O (3 c.c.); the clear solution obtained on heating deposited the *methochloride* (0·9 g.) on long keeping in light yellow, rhombic prisms, m. p. 241—242° after sintering at 238° (Found: C, 68·7; H, 6·0; N, 3·1; Cl, 8·3. $C_{26}H_{26}O_4NCl$ requires C, 69·1; H, 5·8; N, 3·1; Cl, 7·9%).

6-*Hydroxy*-7-*methoxy*-1-(3′-*benzyloxy*-4′-*methoxybenzyl*)-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline.—A solution of the foregoing methochloride (0·7 g.) in 90% EtOH (30 c.c.) was shaken with H in presence of PtO_2–Pt and 70 c.c. were absorbed in 30 min. (theory for $2H_2$, 69 c.c.). The filtered liquid was evaporated in vac., the residual hydrochloride dissolved in 1% KOH aq., and the solution saturated with $KHCO_3$, which pptd. the *base* (0·5 g.). This substance crystallised from EtOH aq. as aggregates of colourless needles, m. p. 52—54° after keeping in vac. over P_2O_5 (Found: C, 74·0; H, 7·1; N, 3·4. $C_{26}H_{29}O_4N$ requires C, 74·4; H, 6·9; N, 3·3%). The base is freely sol. in C_6H_6, $CHCl_3$, EtOAc, acetone, and EtOH, not so readily sol. in Et_2O; it becomes light yellow on exposure to air.

On debenzylation, as described above for the dibenzyl ether, the laudanosoline dimethyl ether, considered to be protosinomenine, was produced. The diphenolic base was isolated as picrolonate, which crystallised from EtOH–AcOH in yellow spindles; m. p. 177—178° (sintering from 170°), alone or mixed with the specimen obtained by the alternative process.

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